(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 308 135 B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 19.11.92 (51) Int. Cl.5: A61K 31/557, A61K 9/06

(21) Application number: 88308299.2

(22) Date of filing: 08.09.88

Divisional application 91108317.8 filed on 08/09/88.

(54) **Ocular hypotensive agents.**

(30) Priority: 18.09.87 JP 235890/87
29.12.87 JP 334037/87

(43) Date of publication of application:
22.03.89 Bulletin 89/12

(45) Publication of the grant of the patent:
19.11.92 Bulletin 92/47

(84) Designated Contracting States:
AT BE CH DE ES FR GR IT LI LU NL SE

(56) References cited:
EP-A- 281 239
EP-A- 284 180
EP-A- 289 349
EP-A- 292 177
EP-A- 0 093 380
EP-A- 0 242 580
FR-A- 2 272 641

JOURNAL OF CHROMATOGRAPHY, vol. 156, 1978, Elsevier Scientific Publ.Co., Amsterdam (NL); W.D.WOODS et al., pp. 131-141.

ARCH. INT. PHARMACODYN, vol. 207, 1974; T.S.CHIANG, pp. 131-138.

ACTA PHYSIOL. SCAND. vol. 66, 1966, pages 509-510; Stockholm, SW E. ANGGARD: "The biological activities of three metabolites of prostaglandin EI"

(73) Proprietor: R-TECH UENO, LTD.
4-8, 2-chome, Koraibashi, Chuo-ku
Osaka-shi, Osaka-fu(JP)

(72) Inventor: Ueno, Ryuzo
10-27 Nango-Cho
Nishinomiya-Shi Hyogo-Ken(JP)
Inventor: Ueno, Ryuji
7-29 Misaku-Cho
Nishinomiya-Shi Hyogo-Ken(JP)
Inventor: Oda, Tomio
1-116-1-202 Midorigaoka
Itami-Shi Hyogo-Ken(JP)

(74) Representative: Atkinson, Peter Birch et al
Marks & Clerk Suite 301 Sunlight House
Quay Street
Manchester M3 3JY(GB)

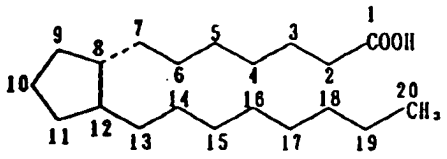
EP 0 308 135 B1

F4

Description

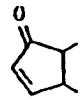
The present invention relates to ocular hypotensive agents which contains 13,14-dihydro-15-keto-prostaglandins.

Prostaglandins (hereinafter referred to as PGs) is the name given to the group of fatty acids which show various physiological activities and which are contained in human and animal tissues and organs. PGs essentially contain the prostanoic acid skeleton of the following formula:



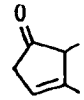
Some synthetic products may also contain the above skeleton with some modification.

PGs are classified into several types according to their five-membered ring, for example,

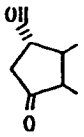


prostaglandins of the A series (PGAs):

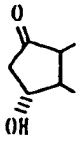
Prostaglandins of the B series (PGBs):



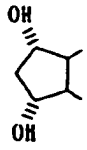
Prostaglandins of the C series (PGCs):



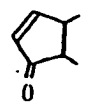
Prostaglandins of the D series (PGDs):



Prostaglandins of the E series (PGEs):

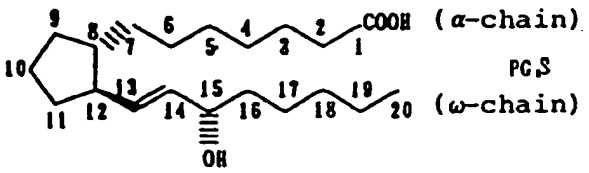


Prostaglandins of the F series (PGFs): and

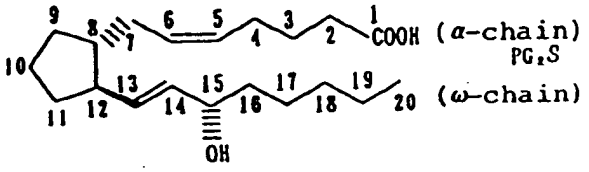


Prostaglandins of the J series (PGJs):

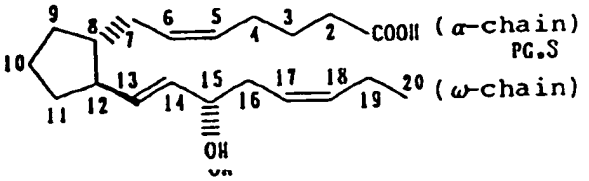
Further, they are classified into PG_1s containing 5,6-single bond:



PG_2s containing 5,6-double bond:



and PG_3s containing 5,6-and 17,18-double bonds:



PGs are known to have various pharmacological and physiological activities, for example, vasodilation, induction of inflammation, platelet aggregation, contraction of uterine muscle and enteron contraction. However, PGs also possesses various other activities. Therefore there are some problems in their use as medicines. That is, when PGs are administered to obtain a single pharmaceutical activity, they often exhibit other activities as side effects. Accordingly, the investigations of PGs as a medicine have aimed to enhance their the main pharmaceutical activity. However, these investigations have been insufficient.

Among PGs, for example, PGAs, PGDs, PGEs, PGFs are known to possess ocular hypotensive potency.

For example, it is disclosed in Japanese Patent Application KOKAI NO. 1418/1984 (claiming a priority based on U.S. Ser. No. 374165 (1982) by Laszlo Z. Bito) that PGF_2 has a high ocular hypotensive activity and that 15-keto-$PGF_{2\alpha}$ also the activity though to a reduced degree. Further Japanese Patent Application KOKAI No. 66122/1988 (claiming priorities based on three U.S. Ser. Nos. 839056 (1986), 892387 (1986) and 022046 (1987)) discloses that PGA, PGB and PGC can be used for a treatment of glaucoma.

However, when these PGs are applied topically to rabbit eyes, they produce a transient ocular hypertensive response. Pronounced conjunctival and iridal hyperemia, and further side effects such as lacrimation, eye mucus and lid closure are also observed. Accordingly, there are some problems associated with the use of PGs as remedies for glaucoma or as ocular hypotensive agents.

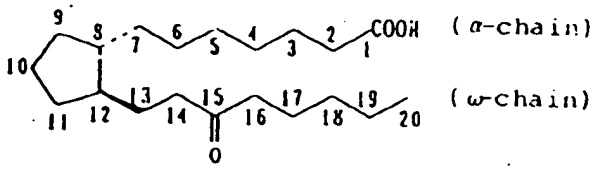
On the other hand, PGs wherein the carbon atoms at the 13-14 positions are saturated and the carbon atom at the 15 position forms a carbonyl group are found to exist in human or animal metabolites. These 13,14-dihydro-15 keto-prostaglandins (hereinafter referred to as 13,14-dihydro-15-keto-PGs) are known to be naturally produced by enzymatic metabolism of the corresponding PGs in vivo. These 13,14-dihydro-15-keto-PGs have been reported as not exhibiting the various physiological activities that PGs possess and to be pharmacologically and physiologically inactive metabolites (see Acta Physiologica Scandinavica, 66, p.509 - (1966).

According to the present invention there is provided the use of 13,14-dihydro-15-keto-prostaglandin A, B, C, D, F or J for the manufacture of a medicament for the treatment of ocular hypertension.

It has been found the compounds defined in the preceding paragraph cause intraocular pressure reduction without the transient ocular hypertensive response that PGs usually show. Further, among 13,14-dihydro-15-keto-PGs, (as either the carboxylic acid, salt, or ester) compounds having a 2,3-double bond, or a 5,6-triple bond, or compounds having substituents at any of C-3, C-6, C-16, C-17, C-19 and/or C-20 positions, or compounds having a lower alkyl or hydroxyalkyl group at the C-9 and/or C-11 position instead of the hydroxyl group, possess enhanced ocular hypotensive potency. These 13,14-dihydro-15-keto-PGs may exhibit an ocular hypotensive effect without transient ocular hypertensive response, and with absolutely no or extremely reduced side effects such as hyperemia. Further, we have found that these 13,14-dihydro-15-keto-PGs are accompanied with no or extremely reduced peculiar central and peripheral physiological activities which are caused by PGs, and further they have no effects on enteron, trachea or bronchus which are characteristic of PGs.

In the present invention, 13,14-dihydro-15-keto-PGs means PGs in which the carbon atoms at the 13-14 positions are saturated and the carbon at the 15 position forms a carbonyl group.

In this description, 13,14-dihydro-15-keto-PGs are named as follows, viz the carbons constituting the α-chain, ω-chain and 5-membered ring are numbered according to the basic skeleton as follows:



That is, in the basic skeleton, the constituent carbon atoms are numbered in such a way that the carboxylic acid carbon atom is C-1, the α-chain contains C-2 - C-7, (the number increasing toward the ring), the five-membered ring contains C-8 - C-12, and the ω-chain contains C-13 - C-20. When there are fewer than 7 carbons of the α-chain, the numbers of the carbons following C-2 should be simply eliminated from 2 to 7 in this order, and when more than 7, the compound is named such that the 'increase' is named as a substituent on the carbon at the 2 position. When the ω-chain contains fewer carbon atoms, they should be numbered correspondingly smaller than 20, and when more than 8, the carbon atoms at the 21 position and thereafter should be regarded as a substituent. As configuration, it is considered according to that of the above essential skeleton unless otherwise described.

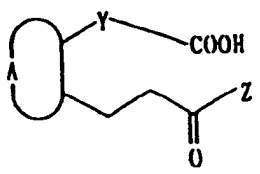
For example, PGD, and PGF mean compounds having a hydroxyl group at the C-9 and/or C-11 positions. In the present invention, PGs include compounds having a group other than hydroxyl group on the C-9 and/or C-11 positions, such compounds being named as 9-dehydroxy-9-substituted or 11-dehydroxy-11-substituted compounds.

13,14-Dihydro-15-keto-PGs used in the present invention may be 13,14-dihydro-15-keto-PG_1s containing a 5,6-single bond, 13,14-dihydro-15-keto-PG_2s containing a 5,6-double bond, 13,14-dihydro-15-keto-PG_3s containing both 5,6- and 17,18-double bonds may be used.

The typical examples of the 13,14-dihydro-15-keto-PGs used in the present invention are shown below:
13,14-dihydro-15-keto-PGA_1s, 13,14-dihydro-15-keto-PGA_2s,
13,14-dihydro-15-keto-PGA_3s, 13,14-dihydro-15-keto-PGB_1s,
13,14-dihydro-15-keto-PGB_2s, 13,14-dihydro-15-keto-PGB_3s,
13,14-dihydro-15-keto-PGC_1s, 13,14-dihydro-15-keto-PGC_2s,
13,14-dihydro-15-keto-PGC_3s, 13,14-dihydro-15-keto-PGD_1s,
13,14-dihydro-15-keto-PGD_2s, 13,14-dihydro-15-keto-PGD_3s,
13,14-dihydro-15-keto-PGF_1s, 13,14-dihydro-15-keto-PGF_2s,
13,14-dihydro-15-keto-PGF_3s, 13,14-dihydro-15-keto-PGJ_1s,
13,14-dihydro-15-keto-PGJ_2s, 13,14-dihydro-15-keto-PGJ_3s.

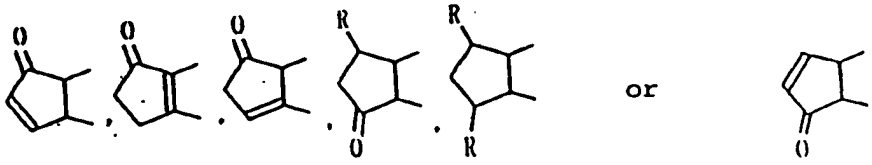
These 13,14-dihydro-15-keto-PGs show strong ocular hypotensive potency without showing transient ocular hypertensive response. Further, side effects such as pronounced conjunctival or iridal hyperemia, lacrimation, and lid closure are either not present or are extremely reduced. Accordingly, these 13,14-dihydro-15-keto-PGs are extremely effective as ocular hypotensive agents. Further, depending on such ocular hypotensive effect, they may be used for glaucoma therapy.

In the present invention, the ocular hypotensive effect is especially pronounced in prostaglandins of the general formula:



[I]

[wherein, A is



(in which R is hydroxyl, hydroxyalkyl or alkyl);
Y is a saturated or unsaturated C_{2-6} hydrocarbon chain (some of the carbon atoms constituting the hydrocarbon chain may form a carbonyl group, and the hydrocarbon chain may be substituted with one or more atoms or groups);
Z is a C_{1-10} saturated or unsaturated hydrocarbon forming a straight-chain, branched-chain or ring (the hydrocarbon may be substituted with atoms or groups)] or physiologically acceptable salts derived from the general formula [I] or those having an esterified carboxyl group.

A saturated or unsaturated C_{2-6} hydrocarbon chain Y includes a straight hydrocarbon chain such as an alkyl, alkenyl, and alkynyl. A hydrocarbon chain with 6 carbons is preferred.

Examples of an unsaturated hydrocarbon chain Y include, for example, PGs in which the carbons at the 2-3 positions or 5-6 positions are joined by an unsaturated bond.

Some of the carbons forming the hydrocarbon chain Y may form a carbonyl group. A typical example includes 6-keto-PG_1s wherein the carbon at the 6 position constitutes a carbonyl group.

The hydrocarbon chain Y may be substituted with one or more atoms or groups. Such atoms or groups include, for example, a halogen atom such as a fluorine, chlorine or bromine atom; an alkyl group such as methyl, ethyl; a hydroxyl group. A typical example is one or more alkyl groups at the 3-carbon atom.

Z means a C_{1-10} saturated or unsaturated hydrocarbon group. The hydrocarbon itself may form a ring or may be substituted with one or more atoms or groups.

As the hydrocarbon group Z, a C_{3-9} straight chain is particularly preferred. A hydrocarbon group with five carbons provides PGs with an ω-chain having eight carbons. Accordingly, as described above, a hydrocarbon Z having more than 6 carbons is assumed to provide a substituent at the 20- carbon atom in the ω-chain (eg, a hydrocarbon having seven carbons provides 20-ethyl-PGs).

The unsaturated bond (if present) may be at any position in Z. However, it is preferred that Z is unsaturated. Examples of the hydrocarbon Z forming a ring include a cyclo-pentyl or cyclohexyl group in which the carbons at 16 or 17 position in the ω-chain may be part of the ring.

Z may be substituted with one or more atoms or groups. Such atoms or groups include a halogen atom such as a fluorine, chlorine or bromine atom; an alkyl group such as a methyl, ethyl, isopropyl or isopropenyl group; an alkoxy group such as a methoxy or ethoxy group; a hydroxyl group; a phenyl group; and a phenoxy group. The position of the substituent atom(s) or group(s) is not limited, but typically, they may be at 16, 17, 19 and/or 20 position in the ω-chain. Particularly preferred are compounds having one or two of the same or different atoms at the C-16 position, for example, a halogen atom such as a fluorine atom or a substituent, for example, an alkyl group such as a methyl, ethyl, hydroxyl phenyl which may contain one or more substituents, benzyl, phenoxy, or cycloalkyl group such as a cyclopentyl or cyclohexyl group which contains the C-16 position as a constituent; compounds having an alkyl group such as methyl at the C-17 or C-19 position; and compounds having an alkyl group such as a methyl, ethyl, isopropyl, isopropenyl or alkoxy group such as a methoxy, ethoxy or propoxy group at the C-20 position.

PGs may include the compounds PGD, PGF which contain a hydroxyl group at the C-9 and/or C-11 position. In the present invention, PGs further include the compounds having a hydroxyalkyl or alkyl group instead of the hydroxyl group at the C-9 and/or C-11 position. Accordingly, the 13,14-dihydro-15-keto-PGs

of the present invention include the compound of the general formula [I], wherein R is a hydroxyl, hydroxyalkyl or alkyl group. Such a hydroxyalkyl group is preferably a hydroxymethyl or 1-hydroxyethyl, 2-hydroxyethyl or 1-methyl-1-hydroxyethyl group. As the alkyl group, a lower alkyl group, especially a methyl or ethyl group is preferred.

The configuration of R for the carbon at the 9 and/or 11 position may be α, β or mixture thereof.

PGs of the present invention may be salts or esters. Such salts include physiologically acceptable salts, for example, those of an alkali metal such as sodium, potassium; those of an alkaline earth metal such as calcium, magnesium; those of an ammonium salt such as ammonia, methylamine, dimethylamine, cyclopentylamine, benzylamine, piperidine, monoethanolamine, diethanolamine, monomethyl-monoethanolamine, tromethamine, lysine, and tetralkylammonium salt. Such an ester includes, for example, methyl, ethyl, propyl, butyl, isopropyl, t-butyl, 2-ethylhexyl, straight or branched-chain alkyl ester which may contain an unsaturated bond; for example, ester having an alicyclic group such as a cyclopropyl, cyclopentyl or cyclohexyl group; an ester containing an aromatic group such as a benzyl or phenyl group (wherein the aromatic group may contain one or more substituents); a hydroxyalkyl or alkoxyalkyl ester such as a hydroxyethyl, hydroxyisopropyl, polyhydroxyisopropyl, methoxyethyl, ethoxyethyl or methoxyisopropyl group; an alkylsilyl ester e.g., a trimethylsilyl or triethylsilyl ester; a tetrahydropyranyl ester.

Preferred esters include, for example, a straight or branched lower alkyl ester such as a methyl, ethyl, propyl, n-butyl, isopropyl or t-butyl ester; or a benzyl ester; a hydroxyalkyl ester such as a hydroxyethyl or hydroxyisopropyl ester.

The carboxyl group at the C-1 position of 13,14-dihydro-15-keto-PGs of the present invention may be any of the above described groups. Among them, esters, especially the C_{1-4} alkyl ester are preferred.

13,14-dihydro-15-keto-PGs of the present invention may include the isomers of the above compounds. Examples of such isomers include keto-hemiacetal tautomers between the C_6-carbonyl and C_9-hydroxyl, or the C_{11}-hydroxyl and C_{15}-carbonyl; optical isomers; and geometrical isomers.

Keto-hemiacetal tautomers between the C_{11}-hydroxyl group and C_{15}-carbonyl may be readily formed especially in 13,14-dihydro-15-keto-PGEs having an electrophilic group such as a fluorine atom at the C-16 position.

A mixture of the isomers, for example, a racemic mixture, tautomers of hydroxyl compound and hemiacetals may show similar effect as that shown by the respective compound.

In the present invention, especially preferred 13,14-dihydro-15-keto-PGs contain a 5,6-single or double bond, or a carbonyl group at the C-6 position. Other preferred compounds are 13,14-dihydro-15-keto-PGs having 20-24 carbon atoms. Still other preferred compounds are 13,14-dihydro-15-keto-PGs wherein the carbon atom at the 16 position is substituted with a halogen atom or an alkyl group. Further preferred compounds are 13-14-dihydro-15-keto-PGs having more than 20 carbons and an alkyl group at C-19 position.

Particularly, the compounds having a C_{1-4} alkyl, (for example, a methyl, ethyl, propyl or butyl group) at the C-20 position (ie having a prolonged ω-chain) show enhanced ocular hypotensive effect with little side effects such as hyperemia. Accordingly, such compounds are preferred.

That is, in 13,14-dihydro-15-keto-PGs used in the present invention, those having an alkyl group at the C-20 position provide a particularly beneficial result, irrespective of the structure of the five-membered ring, or the existence of double bond or other substituents. Particularly, those wherein the alkyl group is ethyl (wherein the ω-chain contains a C_{10} straight chain) show the most pronounced ocular hypotensive effect, scarcely showing side effects such as hyperemia, thereby providing the most preferable product as a whole.

In the present invention, PGs are named according to the prostanoic acid skeleton. If named according to IUPAC, for example, $PGF_{1\alpha}$ corresponds to 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E)-(3S)-3-hydroxy-1-octenyl]-cyclopentyl]-heptanoic acid; $PGF_{2\alpha}$, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E)-(3S)-3-hydroxy-1-octenyl]-cyclopentyl]-5-heptenoic acid; 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester, isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxo-1-decyl)-cyclopentyl]-hept-5-enoate; 13,14-dihydro-15-keto-16-methyl-$PGF_{2\alpha}$ methyl ester, methyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxo-1-nonyl)-cyclopentyl]-hept-5-enoate. Other PGs may also be named in the same way.

13,14-dihydro-15-keto-PGs of the present invention include isomers of the above compounds. Examples of these isomers include keto-hemiacetal tautomers between the C-6 carbonyl and C-9 hydroxyl groups, or the C-11 hydroxyl and C-15 carbonyl groups; optical isomers; and geometrical isomers.

The keto-hemiacetal tautomers between the C-11 hydroxyl and C-15 carbonyl groups may be readily formed, for example, in the case of 13,14-dihydro-15-keto-PGs which contain one or more electrophilic groups such as a fluorine atom at the 16 position. A mixture of isomers (for example, a racemic mixture or a mixture of tautomers of the hydroxy compound with hemiacetals) shows a similar effect as that shown by

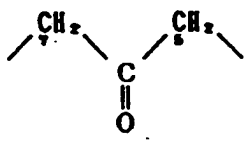
the respective compound.

The above 13,14-dihydro-15-keto-PGs of the present invention may be prepared according to the methods described, for example, in Japanese Patent Application Nos. 63-18326, 63-18327 and 63-108329.

In the process for preparing 13,14-dihydro-15-keto-compound:

A commercially available (-)-Corey lactone, which is used as a starting material, is subjected to Collins oxidation to give an aldehyde. The aldehyde is allowed to react with dimethyl (2-oxoalkyl) phosphonate anion to give an α,β- unsaturated ketone, and the resultant product is reduced to ketone. The carbonyl group of the ketone is allowed to react with a diol to give a ketal (and is thereby protected), then the corresponding alcohol is obtained by elimination of the phenylbenzoyl group, and the resulting hydroxy group is protected with dihydropyran to give a tetrapyranyl ether. Thus, precursors of PGs wherein the ω-chain is 13,14-dihydro-15-keto-alkyl can be obtained.

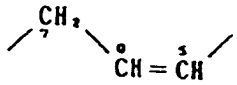
Using the above tetrapyranyl ether as a starting material, 6-keto-PG_1s of the formula:



may be obtained as follows:

The tetrapyranyl ether is reduced using for example diisobutyl aluminium hydride to give a lactol, which is allowed to react with a ylide obtained from (4-carboxybutyl)triphenylphosphonium bromide, and the resultant product is subjected to esterification followed by cyclization, combining the 5,6-double bond and the C-9 hydroxyl group with NBS or iodine, providing a halide. The resultant product is subjected to dehydrohalogenation with for example DBU to give a 6-keto compound, which is subjected to Jones oxidation followed by deprotection to give the desired compound.

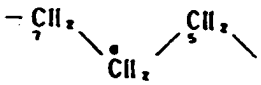
Further, PG_2s of the formula:



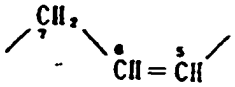
may be obtained as follows:

The above tetrapyranyl ether is reduced to the lactol, which is allowed to react with a ylide obtained from (4-carboxybutyl) triphenylphosphonium bromide to give a carboxylic acid. The resultant product is subjected to esterification followed by Jones oxidation and deprotection to give the desired compound.

In order to obtain PG_1s of the formula:

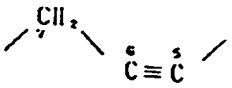


using the above tetrapyranyl ether as a starting material, the procedure described above for forming PG_2s of the formula:

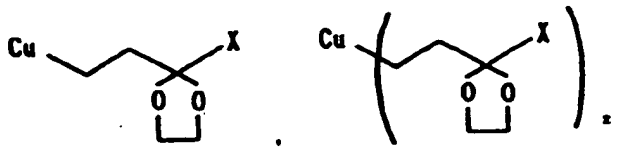


is followed and the 5,6-double bond of the resulting compound is subjected to catalytic reduction followed by deprotection.

To prepare 5,6-dehydro-PG_2s containing a hydrocarbon chain of the formula:



a monoalkyl copper complex or a dialkyl copper complex of the formula:



is subjected to 1,4-addition with 4R-t-butyldimethylsilyloxy-2-cyclopenten-1-one, and the resulting copper enolate is reacted with 6-carboalkoxy-1-iodo-2-hexyne or a derivative thereof.

PGs containing a methyl group instead of a hydroxy group at the C-11 position may be obtained as follows: PGA obtained by Jones oxidation of the hydroxy group at the C-9 position of the 11-tosylate is allowed to react with a dimethyl copper complex to give 11-dehydroxy-11-methyl-PGE. Alternatively, an alcohol obtained after elimination of p-phenylbenzoyl group is converted to a tosylate. An unsaturated lactone obtained by DBU treatment of the tosylate is converted to a lactol. After introduction of an α-chain using the Wittig reaction, the resulting alcohol (C-9 position) is oxidized to give PGA. PGA is allowed to react with dimethyl copper complex to give 11-dehydroxy-11-methyl-PGE. The resultant is reduced using sodium borohydride and the like to give 11-dehydroxy-11-methyl-PGF.

PGs containing a hydroxymethyl group instead of a hydroxyl group at the C-11 position are obtained as follows: 11-dehydroxy-11-hydroxymethyl-PGE is obtained by a benzophenone-sensitized photoaddition of methanol to PGA. The resultant is, for example, reduced using sodium borohydride to give 11-dehydroxy-11-hydroxymethyl-PGF.

16-Fluoro-PGs may be obtained using dimethyl (3-fluoro-2-oxoalkyl) phosphonate anion in the preparation of an α,β- unsaturated ketone. Similarly, 19-methyl-PGs may be obtained using a dimethyl (6-methyl-2-oxoalkyl) phosphonate anion.

The present invention is not to be construed as limited to the above described preparative methods. For example, other procedures for protection, oxidation, and reduction may be employed.

13,14-Dihydro-15-keto-PGs of the present invention can be used for animal and human treatment, and, in general, used for systemic or local application by oral administration, intravenous injection, subcutaneous injection, suppository, collyrium, and oculentum. The dosage varies depending on factors such as type of patient, age, weight, conditions, therapeutic effect, administration route, and treatment time.

The solid composition for oral administration of the present invention includes, for example, tablets, preparations and granules. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone and magnesium aluminate metasilicate. According to the usual work-up, the composition may contain additives other than an inactive diluent, for example, a lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; a stabilizer such as etherified cyclodextrin, for example, a, β- or γ-cyclodextrin, dimethyl-α, dimethyl-β-, trimethyl-β- or hydroxypropyl-β-cyclodextrin, branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin, formylated cyclodextrin, cyclodextrin containing sulfur, mitthoprotol, and phospholipid. When the above cyclodextrins are used, an inclusion compound with cyclodextrins may be sometimes formed to enhance stability. Alternatively, a phospholipid may be sometimes used to form a liposome, resulting in enhanced stability.

Tablets or pills may be coated with a film material which is soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose and hydroxypropylmethyl cellulose phthalate, or with more than two

layers. Further, they may be formed as capsules with absorbable substances such as gelatin.

A liquid composition for oral administration may contain a pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir as well as a generally used inactive diluent, for example, purified water, or ethanol. Such a composition may contain, in addition to the inactive diluent, adjuvants such as wetting agents and suspensions, sweetening agents, flavoring agents, and preservatives.

Other compositions for oral adminstration include a spray formulated by known method, which may contain one or more active ingredients.

Injection for parenteral administration according to the present invention includes a sterile, aqueous or nonaqueous solution, suspension and emulsion.

A diluent for such an aqueous solution and suspension includes, for example, injectable distilled water, physiological saline and Ringer's solution.

A diluent for non-aqueous solution and suspension includes, for example, propylene glycol, polyethylene glycol, vegetable oil such as olive oil, alcohols such as ethanol, and polysorbate. Such a composition may contain adjuvants such as preservatives, wetting agents, emulsifiers, dispersants and stabilizers. These are sterilized, for example, by filtration through a bacteria-holding filter, compounding with germicides, gas sterilization or radio-sterilization. These may be used by preparing a sterile solid composition and dissolving in sterile water or sterile solvent for injection before use.

The collyrium according to the present invention may include a sterile aqueous or non-aqueous solution, or suspension. The diluent for such an aqueous solution or suspension includes, for example, distilled water or a physiological saline. The diluent for the non-aqueous solution or suspension may include an edible oil, liquid paraffin, mineral oil, propylene glycol, and p-octyldodecanol. Further, in order to make the compositions isotonic to tears, isotonic agents such as sodium chloride, benzalkonium chloride, phedrine chloride, procaine chloride, chloram phenicol, and sodium citrate may be used. Alternatively, in order to maintain the pH value constant, a buffer such as a borate or phosphate buffer may be used. Moreover, stabilizers such as sodium sulfite, sodium carbonate, EDTA, propylene glycol; thickening agents such as glycerin, carboxymethyl cellulose, carboxyvinyl polymer; diluents such as polysorbate, macrogols, alminum monostearate; preservatives such as paraben, benzyl alcohol, sorbic acid; and further resolvents, vehicles may be compounded. These may be sterilised, for example, by the filtration through a bacteria-holding fitter or heat sterilisation. In the preparation of collyrium, pH value and ion strength of the agent are especially important, and they may be optionally adjusted to the optimal value depending on the types and amounts of other active ingredients or additives used.

The oculentum according to the present invention may contain vaseline, selen 50, pastibase, macrogols as a base, and surfactant such as polysorbate, Tween®, purified lanolin, jelly such as carboxymethyl cellulose, methylcellulose, carboxyvinyl polymer to enhance hydrophilism.

The ocular hypotensive agent of the present invention may be used as a remedy for glaucoma utilizing its ocular hypotensive potency. When used as the remedy for treatment of glaucoma, the present agents may be compounded with conventional cholinergic ocular hypotensive agents (e.g., pilocarpine, carbachol, which possesses excellent miotic activity) anticholinesterases (e.g., demecarium, D.F.P., echothiophate), physostigmine salicylate, pilocarpine hydrochloride as miotics, mannitol, glycerin, isosorbide as hyperosmotic agent for intravenous injection, chlorobutanol, benzalkonium chloride, propylparabene, methylparaben, ethylparaben, butylparaben as preservatives for collyrium, penicillin, sulfonamide, chloramphenicol, cortisone, chlorpheniramine for prevention and treatment of other inflammation.

The present invention will be illustrated in the following examples.

Preparations

Preparations of 13,14-dihydro-15-keto-20-ethyl-PGA_2 isopropyl ester, 13,14-dihydro-15-keto-20-ethyl-PGE_2 isopropyl ester and 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester (cf. Preparation chart I):

1) Preparation of 1S-2-oxa-3-oxo-6R-(3-oxo-1-trans-decenyl)-7R-(4-phenylbenzoyloxy)-cis-bicyclo[3.3.0]-octane (3):

Commercially available (-)-Corey lactone (1) (7 g) was subjected to Collins oxidation in dichloromethane to give aldehyde (2). The resultant was allowed to react with dimethyl (2-oxononyl)-phosphonate (4.97 g) anion to give 1S-2-oxa-3-oxo-6R-(3,3-ethylendioxy-1-trans-decenyl)-7R-(4-phenylbenzoyloxy)-cis-bicyclo[3.3.0]-octane (3).

2) Preparation of 1S-2-oxa-3-oxo-6R-(3-oxodecyl)-7R-(4-phenylbenzoyloxy)-cis-bicyclo[3.3.0]-octane (4):

Unsaturated ketone (3) (7.80 g) was reduced in ethyl acetate (170 ml) using 5% Pd/C under hydrogen atmosphere. The product obtained after the usual work-up (4) was used in the following reaction.

3) Preparation of 1S-2-oxa-3-oxo-6R-(3,3-ethylenedioxy-decyl)-7R-(4-phenylbenzoyloxy)-cis-bicyclo-[3.3.0]-octane (5):

Saturated ketone (4) was converted to ketal (5) in dry benzene (150 ml) using ethylene glycol and p-toluenesulfonic acid (catalytic amount).

4) Preparation of 1S-2-oxa-3-oxo-6R-(3,3-ethylenedioxy-decyl)-7R-hydroxy-cis-bicyclo[3.3.0]-octane (6):

To a solution of ketal (5) in absolute methanol (150 ml) was added potassium carbonate (2.73 g). The mixture was stirred overnight at room temperature. After neutralization with acetic acid, the resultant product was concentrated under reduced pressure. The resulting crude product was extracted with ethyl acetate. The organic layer was washed with a dilute aqueous solution of sodium bicarbonate and a saline, and dried. The crude product obtained after evaporation was chromatographed to give alcohol (6).

Yield; 3.31 g

5) Preparation of lactol (7):

Alcohol (6) (0.80 g) was reduced in dry toluene (8 ml) using DIBAL-H at -78 °C to give lactol (7).

6) Preparation of 13,14-dihydro-15,15-ethylenedioxy-20-ethyl-$PGF_{2\alpha}$ (8):

A DMSO solution of lactol (7) was added to ylide prepared from (4-carboxybutyl)-triphenylphosphonium bromide (3.65 g). The reaction mixture was stirred overnight to give carboxylic acid (8).

7) Preparation of 13,14-dihydro-15,15-ethylenedioxy-20-ethyl-$PGF_{2\alpha}$ isopropyl ester (9):

Carboxylic acid (8) was converted to 13,14-dihydro-15,15-ethylenedioxy-20-ethyl-$PGF_{2\alpha}$ isopropyl ester (9) using DBU and isopropyl iodide in acetonitrile.

Yield; 0.71 g

8) Preparation of 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester (10):

13,14-Dihydro-15,15-ethylenedioxy-20-ethyl-$PGF_{2\alpha}$ isopropyl ester (9) (0.71 g) was kept in acetic acid/THF/water (3/1/1) at 40 °C for 3 hours. The crude product obtained after concentration under reduced pressure was chromatographed to give 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester (10).

Yield; 0.554 g

9) Preparation of 13,14-dihydro-15-keto-20-ethyl-PGA_2 isopropyl ester (12):

A solution of 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester (10) (0.125 g) and p-toluenesulfonyl chloride (0.112 g) in pyridine (5 ml) was maintained at 0 °C for 2 days. According to the usual work-up, tosylate (11) was obtained.

Tosylate (11) was subjected to Jones oxidation in acetone (8 ml) at -25 °C. The crude product obtained after the usual work-up was chromatographed to give 13,14-dihydro-15-keto-20-ethyl-$PGA_{2\alpha}$ isopropyl ester (2).

Yield; 0.060 g

10) Preparation of 13,14-dihydro-15,15-ethylenedioxy-20-ethyl-11-t-butyldimethylsiloxy-$PGF_{2\alpha}$ isopropyl ester (13):

13,14-Dihydro-15,15-ethylenedioxy-20-ethyl-$PGF_{2\alpha}$ isopropyl ester (9) (3.051 g) was dissolved in dry N,N-dimethylformamide (25 ml), t-butyldimethylsilyl chloride (1.088 g) and imidazole (0.49 g) was added thereto. The resultant was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the resulting crude product was chromatographed to give 13,14-dihydro-15,15-ethylenedioxy-20-ethyl-11-t-butyldimethylsiloxy-$PGF_{2\alpha}$ isopropyl ester (13).

Yield; 2.641 g

11) Preparation of 13,14-dihydro-15,15-ethylenedioxy-20-ethyl-11-t-butyldimethylsiloxy-PGE_2 isopropyl ester (14):

13,14-Dihydro-15,15-ethylenedioxy-20-ethyl-11-t-butyldimethylsiloxy-$PGF_{2\alpha}$ isopropyl ester (13) (1.257 g) was subjected to Jones oxidation at -40 °C. After the usual work-up, the resulting crude product was chromatographed to give 13,14-dihydro-15,15-ethylenedioxy-20-ethyl-11-t-butyl-dimethylsiloxy-PGE_2 isopropyl ester (14).

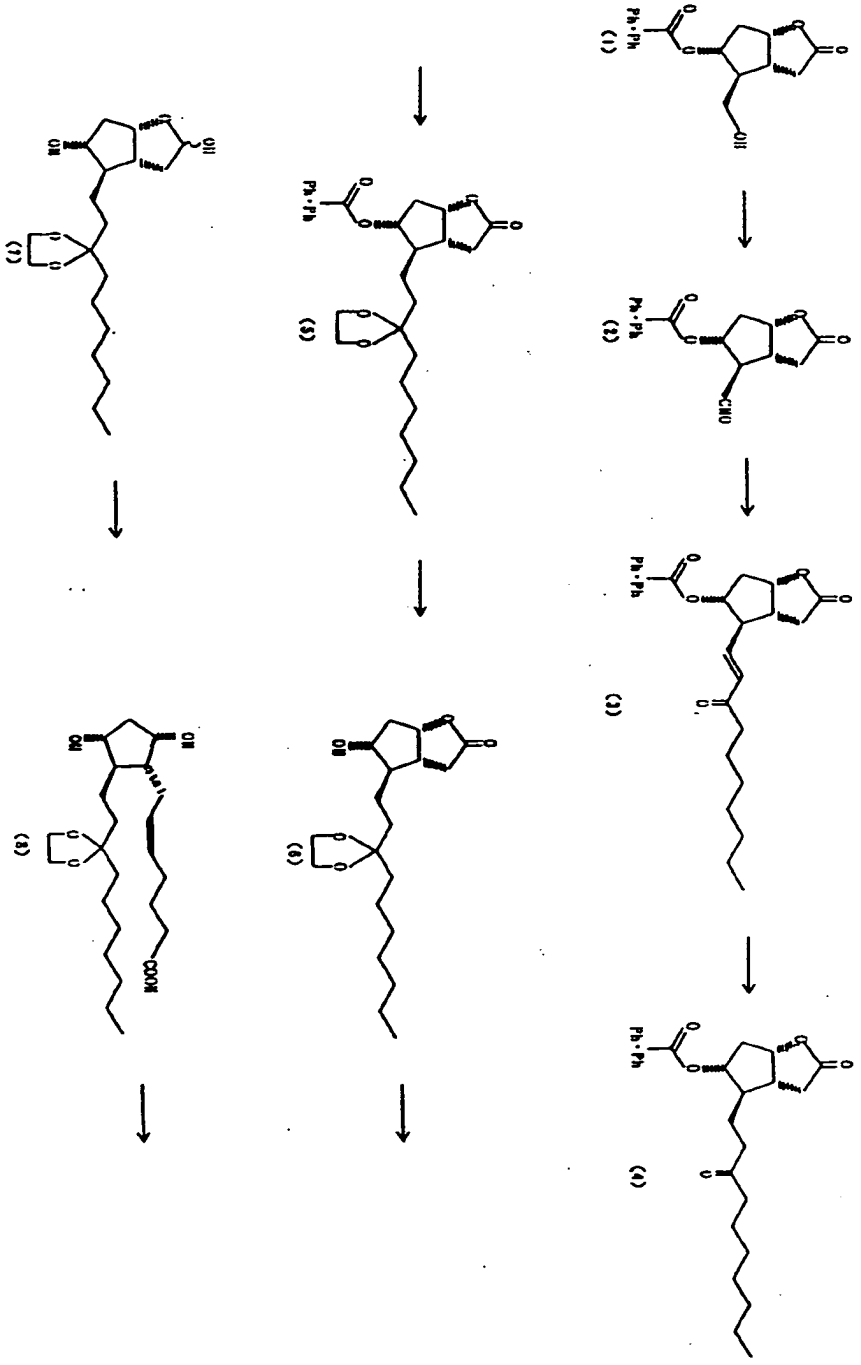
Yield; 1.082 g

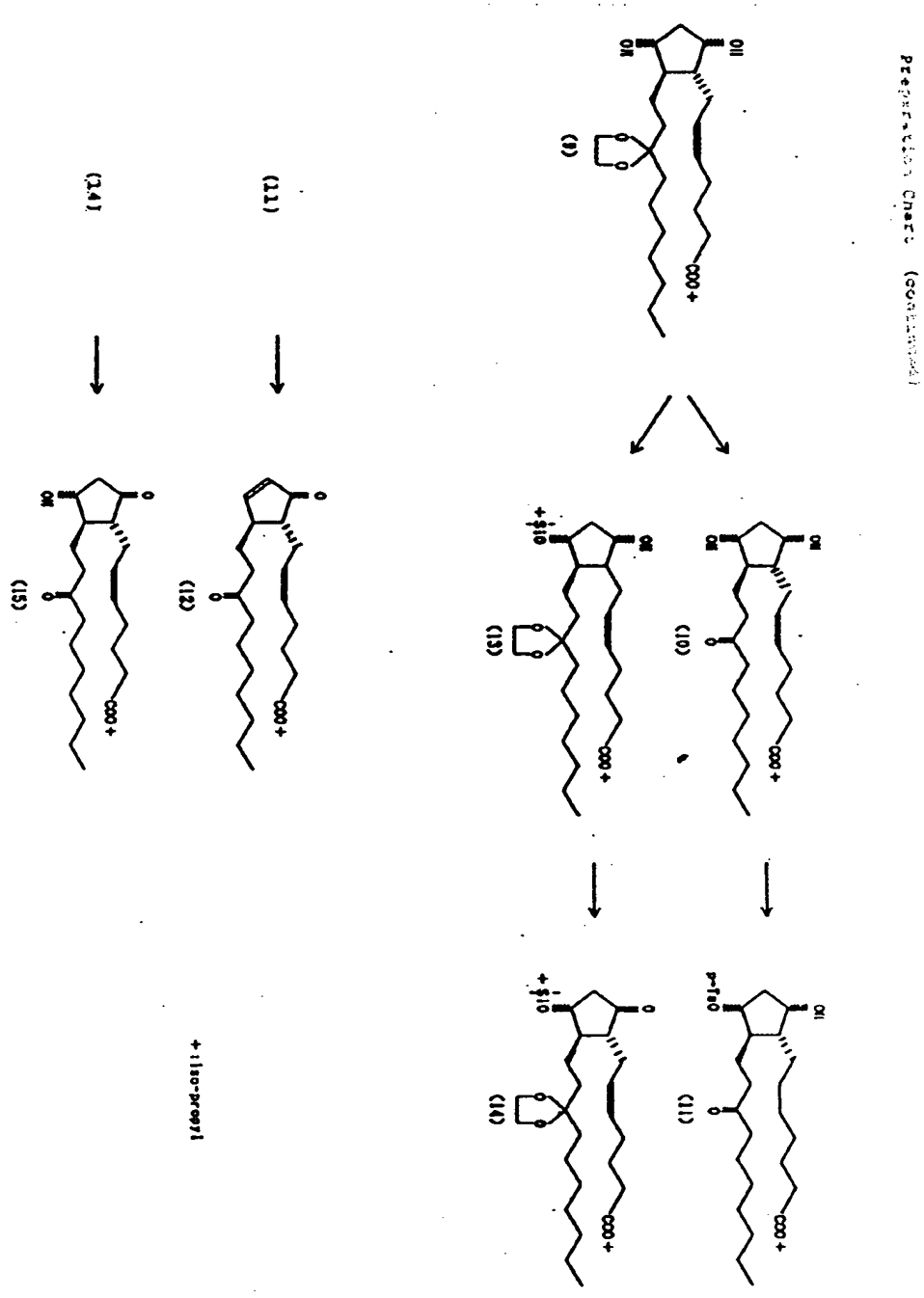
12) Preparation of 13,14-dihydro-15-keto-20-ethyl-PGE_2 isopropyl ester (15):

To a solution of 13,14-dihydro-15,15-ethylenedioxy-20-ethyl-11-t-butyldimethylsiloxy-PGE_2 isopropyl ester (14) in acetonitrile was added hydrofluoric acid (46% aqueous solution). The mixture was stirred at room temperature for 40 minutes. The crude products obtained after usual work-up was chromatographed to give 13,14-dihydro-15-keto-20-ethyl-PGE_2 isopropyl ester (15).

Yield; 0.063 g (97 %)

Preparation Chart





Example 1

For the purpose of tonometry, Japanese White male rabbits (2.5 - 3.0 Kg) were fixed on braces. After topical anesthetization with 0.4 % oxybuprocaine hydrochloride, intraocular pressure was measured using a pneumatic applanation tonometer (manufactured by Japan Alcon). After the topical application of 50 ul of

the suspensions of the test drugs in a physiological saline to one eye, the intraocular pressure was measured and the intraocular pressure reduction (%) caused by each test drug was calculated. At the same time, the extent of conjunctival hyperemia was observed. The results are shown in Table 1.

*** The extent of conjunctival hyperemia:**

-: scarcely observed

±: extremely weak hyperemia

+: slight hyperemia

++: pronounced hyperemia

+++: severe hyperemia

Table 1 (1)

Test Drug	Dose (µg/eye)	Percent change of IOP	Hyperemia
(1)	100	22	±
(2)	100	26	+
(3)	100	24	+
(4)	100	30	+
(5)	100	31	-
(6)	100	33	-
(7)	50	23	-
(8)	50	27	-
(9)	100	40	++

Test drugs:

(1) 13,14-dihydro-15-keto-PGA_1 methyl ester

(2) 13,14-dihydro-15-keto-PGA_1 isopropyl ester

(3) 13,14-dihydro-15-keto-PGA_2 ethyl ester

(4) 13,14-dihydro-15-keto-PGA_2 isopropyl ester

(5) 13,14-dihydro-15-keto-20-ethyl-PGA_1 methyl ester

(6) 13,14-dihydro-15-keto-20-ethyl-PGA_1 isopropyl ester

(7) 13,14-dihydro-15-keto-20-ethyl-PGA_2 methyl ester

(8) 13,14-dihydro-15-keto-20-ethyl-PGA_2 isopropyl ester

(9) PGA_2

Table 1 (2)

Test Drug	Dose (µg/eye)	Percent change of IOP	Hyperemia
(10)	250	7	+
(11)	250	10	+
(12)	250	15	+
(13)	250	20	+
(14)	250	21	-
(15)	250	23	-
(16)	100	18	-
(17)	100	20	-
(18)	250	25	++

Test drugs:

(10) 13,14-dihydro-15-keto-PGB_1 methyl ester

(11) 13,14-dihydro-15-keto-PGB_1 isopropyl ester

(12) 13,14-dihydro-15-keto-PGB_2 methyl ester

(13) 13,14-dihydro-15-keto-PGB_2 isopropyl ester

(14) 13,14-dihydro-15-keto-20-ethyl-PGB_1 methyl ester

(15) 13,14-dihydro-15-keto-20-ethyl-PGB_1 isopropyl ester

(16) 13,14-dihydro-15-keto-20-ethyl-PGB_2 methyl ester

(17) 13,14-dihydro-15-keto-20-ethyl-PGB_2 isopropyl ester

(18) PGB_2

Table 1 (3)

Test Drug	Dose (µg/eye)	Percent change of IOP	Hyperemia
(19)	250	8	+
(20)	250	11	+
(21)	250	18	+
(22)	250	20	+
(23)	250	20	-
(24)	250	22	-
(25)	100	21	-
(26)	100	25	-
(27)	250	23	++

Test drugs:

(19) 13,14-dihydro-15-keto-PGC_1 methyl ester

(20) 13,14-dihydro-15-keto-PGC_1 isopropyl ester

(21) 13,14-dihydro-15-keto-PGC_2 methyl ester

(22) 13,14-dihydro-15-keto-PGC_2 isopropyl ester

(23) 13,14-dihydro-15-keto-20-ethyl-PGC_1 methyl ester

(24) 13,14-dihydro-15-keto-20-ethyl-PGC_1 isopropyl ester

(25) 13,14-dihydro-15-keto-20-ethyl-PGC_2 methyl ester

(26) 13,14-dihydro-15-keto-20-ethyl-PGC_2 isopropyl ester

(27) PGC_2

Table 1 (4)

Test Drug	Dose (µg/eye)	Percent change of IOP	Hyperemia
(28)	250	15	±
(29)	250	17	±
(30)	250	20	±
(31)	250	18	±
(32)	250	21	±
(33)	250	25	±
(34)	250	23	±
(35)	100	13	+
(36)	250	28	±
(37)	250	30	±
(38)	250	24	±
(39)	250	28	±
(40)	250	31	±
(41)	100	18	-
(42)	100	20	-
(43)	100	25	-

Test drugs:

(28) 13,14-dihydro-15-keto-PGD_1 methyl ester

(29) 13,14-dihydro-15-keto-PGD_1 ethyl ester

(30) 13,14-dihydro-15-keto-PGD_2 ethyl ester

(31) 13,14-dihydro-15-keto-PGD_2 n-butyl ester

(32) 13,14-dihydro-15-keto-5,6-dehydro-PGD_2 methyl ester

(33) 13,14-dihydro-15-keto-5,6-dehydro-9β-PGD_2

(34) 13,14-dihydro-15-keto-5,6-dehydro-9β-PGD_2 methyl ester

(35) 13,14-dihydro-15-keto-16R,S-fluoro-PGD_2 methyl ester

(36) 13,14-dihydro-15-keto-16,16-dimethyl-PGD_2 methyl ester

(37) 13,14-dihydro-15-keto-19-methyl-PGD_2 methyl ester

(38) 13,14-dihydro-15-keto-20-methoxy-PGD_2

(39) 13,14-dihydro-15-keto-20-methoxy-PGD_2 n-butyl ester

(40) 13,14-dihydro-15-keto-16R,S-methyl-20-methoxy-PGD_2 methyl ester

(41) 13,14-dihydro-15-keto-20-ethyl-PGD_1 methyl ester

(42) 13,14-dihydro-15-keto-20-ethyl-PGD_1 ethyl ester

(43) 13,14-dihydro-15-keto-20-ethyl-PGD_2 methyl ester

Table 1 (4) (continued)

Test Drug	Dose (μg/eye)	Percent change of IOP	Hyperemia
(44)	100	23	-
(45)	100	20	-
(46)	250	28	+++

Test drugs:

(44) 13,14-dihydro-15-keto-20-ethyl-PGD_2 ethyl ester

(45) 13,14-dihydro-15-keto-20-methoxyethyl-PGD_2 methyl ester

(46) PGD_2

Table 1 (5)

Test Drug	Dose (µg/eye)	Percent change of IOP	Hyperemia
(74)	100	28	+
(75)	100	22	+
(76)	100	33	+
(77)	100	38	+
(78)	20	25	+
(79)	10	42	±
(80)	100	41	+
(81)	250	21	+
(82)	250	40	+
(83)	100	33	±
(84)	25	17	-
(85)	50	28	-
(86)	50	28	-
(87)	50	25	-
(88)	50	23	-
(89)	250	23	+

Test drugs:

(74) 13,14-dihydro-15-keto-$PGF_{1\alpha}$ ethyl ester

(75) 13,14-dihydro-15-keto-$PGF_{2\alpha}$ methyl ester

(76) 13,14-dihydro-15-keto-$PGF_{2\alpha}$ ethyl ester

(77) 13,14-dihydro-15-keto-9β,11α-PGF_2 methyl ester

(78) 13,14-dihydro-15-keto-16R,S-fluoro-$PGF_{2\alpha}$

(79) 13,14-dihydro-15-keto-16R,S-fluoro-$PGF_{2\alpha}$ methyl ester

(80) 13,14-dihydro-15-keto-16R,S-fluoro-11-dehydroxy-11R-methyl-$PGF_{2\alpha}$ methyl ester

(81) 13,14-dihydro-15-keto-16,16-dimethyl-$PGF_{2\alpha}$ ethyl ester

(82) 13,14-dihydro-15-keto-17S-methyl-$PGF_{2\alpha}$ ethyl ester

(83) 13,14-dihydro-15-keto-20-ethyl-$PGF_{1\alpha}$ methyl ester

(84) 13,14-dihydro-15-keto-20-ethyl $PGF_{2\alpha}$

(85) 13,14-dihydro-15-keto-20-ethyl $PGF_{2\alpha}$ methyl ester

(86) 13,14-dihydro-15-keto-20-ethyl $PGF_{2\alpha}$ ethyl ester

(87) 13,14-dihydro-15-keto-20-ethyl $PGF_{2\alpha}$ isopropyl ester

(88) 13,14-dihydro-15-keto-20-ethyl $PGF_{2\alpha}$ n-butyl ester

(89) 13,14-dihydro-15-keto-20-methyl $PGF_{2\alpha}$ methyl ester

Table 1 (5) (continued)

Test Drug	Dose (µg/eye)	Percent change of IOP	Hyperemia
(90)	250	25	±
(91)	250	26	-
(92)	25	43	±
(93)	10	26	±
(94)	250	30	-
(95)	250	18	-
(96)	100	46	+++ *
(97)	25	27	+++ *
(98)	25	31	+++ *

* : Lid closure and lacrimation were observed.

Test drugs:

(90) 13,14-dihydro-15-keto-20-n-propyl-$PGF_{2\alpha}$ methyl ester

(91) 13,14-dihydro-15-keto-20-n-butyl-$PGF_{2\alpha}$ methyl ester

(92) 13,14-dihydro-15-keto-20-ethyl-16R,S-fluoro-$PGF_{2\alpha}$

(93) 13,14-dihydro-15-keto-20-ethyl-16R,S-fluoro-$PGF_{2\alpha}$ methyl ester

(94) 13,14-dihydro-15-keto-20-ethyl-11-dehydroxy-11R-methyl-$PGF_{2\alpha}$ methyl ester

(95) 13,14-dihydro-15-keto-20-ethyl-16R,S-fluoro-11-dehydroxy-11R-methyl-$PGF_{2\alpha}$ methyl ester

(96) $PGF_{2\alpha}$

(97) $PGF_{2\alpha}$ methyl ester

(98) $PGF_{2\alpha}$ isopropyl ester

The n.m.r. of the above compounds used in the Example 1 and Mass are shown hereinafter:

H n.m.r. was determined (using heavy chloroform as a solvent) by a R-90H NMR spectrometer available from Hitachi Seisakusho.

Mass was determined by a M-80B mass spectrometer available from Hitachi Seisaku-sho;

EI method: at ionization patential of 70 eV, SIMS method: silver plate-glycerin matrix.

Compound (3)

δ : 0.88(3H, t, J=6Hz), 1.25(3H, t J=7Hz), 1.10 - 2.75(22H, m), 4.11(2H, q, J=7Hz), 5.37(2H, m), 6.12(1H, dd, J=6Hz, J=2.5Hz), 7.53(1H, dd, J=6Hz, J=3Hz)

Compound (8)

δ : 0.86(3H, t, J=5.5Hz), 1.21(6H, d, J=6Hz), 1.05-2.75(26H, m), 4.96(1H, hept, J=6Hz), 5.37(2H, m), 6.09-(1H, dd, J=6Hz, J=2Hz, 7.50(1H, J=6Hz, J=2.5Hz)

Mass(EI) m/z 404(M^+), 345(M^+ - i- C_3H_7O)

Compound (30)

δ : 0.89(3H, t, J=6Hz), 1.26(3H, t, J=7Hz), 1.06 - 2.93(25H, m), 4.13(2H, q, J=7Hz), 4.41(1H, m), 5.47(2H, m)

Compound (34)

δ : 0.89(3H, t, J=6Hz), 1.09 - 2.96(25H, m), 3.63(3H, s), 4.19(1H, m)

Compound (35)

δ : 0.91(3H, t, J=6Hz), 1.1 - 2.93(23H, m), 3.64(3H, s), 4.3 - 4.5(1.5H, m), 4.98(0.5H, dd, J=6Hz), 5.50(2H, m)

Mass(SIMS) m/z 385$(M+H)^+$, 387(M^+ + 1-H_2O), 365(M^+ + 1-HF)

Compound (37)

δ : 0.86(6H, d, J=7Hz), 0.94 - 2.90(24H, m), 3.64(3H, s), 4.38(1H, m), 5.43(2H, m)
Mass(EI) m/z 380(M^+), 362(M^+-H_2O), 331, 234, 222

Compound (40)

δ : 1.05(3H, d, J=7Hz), 0.80 - 2.83(24H, m), 3.28(3H, s), 3.32(2H, t, J=6Hz), 3.64(3H, s), 4.29 - 4.47(1H, m), 5.44(2H, m)

Compound (45)

δ : 1.10 - 2.95(29H, m), 3.30(3H, s), 3.33(2H, t, J=6Hz), 3.66(3H, s), 4.38(1H, m), 5.44(2H, m)

Compound (83)

δ : 0.87(3H, t, J=6Hz), 1.15 - 2.70(34H, m), 3.63(3H, s), 3.86(1H, m), 4.15(1H, m)
Mass(EI) m/z 398(M^+),380(M^+-18),362,349

Compound (84)

δ : 0.86(3H, t, J=6Hz), 1.15 - 2.70(28H, m), 3.85(1H, m), 4.12(1H, m), 5.10 - 5.75(5H, m)
Mass(EI) m/z 364(M^+-18), 346

Compound (85)

δ : 0.87(3H, t, J=6Hz), 1.10 - 2.65(30H, m), 3.63(3H, s), 3.85(1H, m), 4.13(1H, m), 5.38(2H, m)
Mass(SIMS) m/z 397(M^+ + 1), 379(M^+ + 1-H_2O), 361(M^+ + 1-2H_2O), 345,330

Compound (86)

δ : 0.87(3H, t, J=6Hz), 1.24(3H, t, J=7Hz), 1.10 - 2.95(30H, m), 3.85(1H, m), 4.08(2H, q, J=7Hz), 3.93 - 4.25(1H, m), 5.38(2H, m)
Mass(EI) m/z 410(M^+),392(M^+-18),374

Compound (87)

δ : 0.87(3H, t, J=6Hz), 1.22(6H, d, J=6.5Hz), 1.10 - 2.75(30H, m), 3.85(1H, m), 4.13(1H, m), 4.95(1H, hept, J=6.5Hz), 5.38(2H, m)
Mass(EI) m/z 424(M^+),406(M^+-18),388,347

Compound (88)

δ : 0.70 - 1.03(6H, m), 1.10 - 3.05(34H, m), 3.84(1H, m), 4.03(2H, t, J=6.5Hz), 4.10(1H, m), 5.38(2H, m)
Mass(EI) m/z 420(M^+),402(M^+-18),376,347

Compound (89)

δ : 0.87(3H, t, J=6Hz), 1.15 - 2.70(28H, m), 3.62(3H, s), 3.83(1H, m), 4.12(1H, m), 5.37(2H, m)
Mass(SIMS) m/z 383(M^+ + 1), 365(M^+ + 1-18), 347

Compound (90)

δ : 0.87(3H, t, J=6Hz), 1.10 - 2.70(32H, m), 3.63(3H, s), 3.85(1H, m), 4.12(1H, m), 5.38(2H, m)

Compound (91)

δ : 0.87(3H, t, J=6Hz), 1.10 - 2.70(34H, m), 3.63(3H, s), 3.83(1H, m), 4.12(1H, m), 5.38(2H, m)

Compound (92)

δ : 0.87(3H, t, J=6Hz), 1.10 - 2.90 (26H, m), 3.87(1H, m), 4.12(1H, m), 4.43(0.5H, m), 4.50 - 5.10(3H, brs),4.99(0.5H, m), 5.38(2H, m)
Mass(EI) m/z 400(M^+), 382(M^+), 382(M^+-18),362,344

Compound (94)

δ : 0.87(3H, t, J=5.5Hz), 1.06(3H, d, J=6Hz), 1.15 - 2.55(30H, m), 3.63(3H, s), 4.08(1H, m), 5.38(2H, m)
Mass(EI) m/z 394(M^+), 375(M^+-18), 358,344

Compound (95)

δ : 0.88(3H, t, J=6Hz), 1.08(3H, d, J=6Hz), 1.15 - 2.75(28H, m), 3.63(3H, s), 4.09(1H, m), 4.42(0.5H, m), 4.97(0.5H, m), 5.38(2H, m)
Mass(EI) m/z 412(m^+), 394(M^+-18)

Example 2

For the purpose of tonometry, Japanes White male rabbits (2.5 Kg - 3.0 Kg) were fixed on braces. After anesthetization by topical application of 0.4 % oxybuprocaine hydrochloride, the intraocular pressure was determined using a pheumatic applanation tonometer (manufactured by Japan Alcon K.K.).

The test drugs were suspended in a physiological saline, and a 50 µl aliquot (25 µg/eye of the test drug) was topically applied to one eye, while the other eye received physiological saline. At every 0.5 hr after topical application, up to 2 hr, the intraocular pressure was measured and side effects were observed and assessed. In this experiment, 6 rabbits per group were used, and mean value of the intraocular pressure of the treated eye (the change (mmHg) provided that the intraocular pressure at 0 hr is 0) and rating of the assessment of the side effects at each time were determined. The side effects were rated according to the following standard.

The results are shown in Tables 2 and 3.

Table 2

(Charge in intraocular pressure; Means ± S.E. mmHg)				
Test Drug	Time (hr)			
	0.5	1.0	1.5	2.0
1	-1.7±0.5	-3.5±1.0	-2.5±1.4	-1.2±1.8
4	+4.0±1.1	+0.8±1.4	+0.5±1.0	-0.5±1.9
2	-2.9±0.7	-5.4±1.5	-6.4±1.1	-6.3±1.1
5	+5.3±0.8	+10.3±0.4	+5.4±1.4	+0.2±1.4
3	-2.3±1.0	-4.3±1.9	-4.8±1.1	-4.8±0.7
6	+2.2±1.1	+3.8±2.5	+1.5±1.9	-1.0±1.8

Table 3

(Evaluation of side effects)				
Test Drug	Time (hr)			
	0.5	1.0	1.5	2.0
1	2.2±0.2	2.0±0.3	1.5±0.2	1.2±0.4
4	3.2±0.4	3.0±0.6	2.8±0.5	2.5±0.3
2	2.8±0.3	3.1±0.3	2.7±0.4	2.2±0.5
5	5.0±0.0	5.2±0.2	5.0±0.0	4.8±0.2
3	2.0±0.4	2.3±0.6	2.0±0.5	1.7±0.7
6	5.0±0.0	5.2±0.2	5.3±0.2	5.3±0.3

Standard of the evaluation of the side effects (ocular response)

Scale for Scoring Ocular Lesions

1) Cornea

A) Opacity-degree of density (area most dense taken for reading)

No Opacity	0
Scattered or diffuse area, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris invisible	4

B) Area of cornea involved

One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

A x B x 5 Total maximum = 80

2) Iris

A) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, hemorrhage, gross destruction (any or all of these)	2

A x 5 Total maximum = 10

3) Conjunctivae

A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids about half closed to completely closed	4

C) Discharge

No discharge	0
Any amount different from normal (dose not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs, and considerable area around the eye	3

Score (A' + B + C) x 2 Total maximum = 20

Test Drugs :

1. 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$
2. 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ methyl ester
3. 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester
4. $PGF_{2\alpha}$
5. $PGF_{2\alpha}$ methyl ester
6. $PGF_{2\alpha}$ isopropyl ester

As is obvious from above results, 13,14-dihydro-15-keto-20-alkyl-PGs including 13,14-dihydro-15-keto-20-ethyl-PGF_2s cause intraocular pressure reduction without transient ocular hypertensive response connected with PGs including PGF_2s. Esters are proved to have a stronger tendency to cause intraocular pressure reduction than carboxyl acid type. Compared with PGs including PGF_2s, 13,14-dihydro-15-keto-20-alkyl-PGs including 13,14-dihydro-15-keto-20-ethyl-PGF_2s are accompanied with extremely reduced side effects, which are hardly detectable.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE

1. The use of 13,14-dihydro-15-keto-prostaglandin A, B, C, D, F or J for the manufacture of a medicament for the treatment of ocular hypertension.

2. The use according to Claim 1, wherein the carboxyl group at the end of the α-chain in the 13,14-dihydro-15-keto-prostaglandin is in the form of an alkyl ester.

3. The use according to Claim 1, wherein the 13,14-dihydro-15-keto-prostaglandin is in the form of 20-alkyl having an alkyl group at the C-20 position.

4. The use as claimed in Claim 1, wherein the 13,14-dihydro-15-keto-prostaglandin is a 13,14-dihydro-15-keto-20-ethyl-prostaglandin.

5. The use as claimed in Claim 1, wherein the 13,14-dihydro-15-keto-prostaglandin is a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F.

6. The use as claimed in Claim 1, wherein the 13,14-dihydro-15-keto-prostaglandin is a 13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_{2\alpha}$ isopropyl ester.

7. Use of 13,14-dihydro-15-keto-prostaglandin A, B, C, D, F or J for the manufacture of medicament for treatment of glaucoma.

Claims for the following Contracting States : ES, GR

1. A method of producing an ocular hypotensive agent comprising admixing one of 13,14-dihydro-15-keto-prostaglandin A, B, C, D, F or J and a pharmaceutically acceptable carrier.

2. A method as claimed in claim 1, wherein the carboxyl group at the end of the a-chain in the 13,14-dihydro-15-keto-prostaglandin is in the form of an alkyl ester.

3. A method as claimed in claim 1, wherein the 13,14-dihydro-15-keto-prostaglandin is in the form of 20-alkyl having an alkyl group at the C20 position.

4. A method as claimed in claim 1, wherein the 13,14-dihydro-15-keto-prostaglandin is a 13,14-dihydro-15-keto-20-ethyl-prostaglandin

5. A method as claimed in claim 1, wherein the 13,14-dihydro-15-keto-prostaglandin is a 13,14-dihydro-15-keto-20-ethyl-prostaglandin F.

6. A method as claimed in claim 1, wherein the 13,14-dihydro-15-keto-prostaglandin is a 13,14-dihydro-15-keto-20-ethyl-prostaglandin $F_{2\alpha}$ isopropyl ester.

7. A method of producing an agent for the treatment of glaucoma agent comprising admixing one of 13,14-dihydro-15-keto-prostaglandin A, B, C, D, F or J and a pharmaceutically acceptable carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE

1. Verwendung von 13,14-Dihydro-15-keto-prostaglandin A, B, C, D, F oder J für die Herstellung eines Arzneimittels für die Behandlung von Okularhypertonie.

2. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß die Carboxylgruppe am Ende der α-Kette in dem 13,14-Dihydro-15-keto-prostaglandin in Form eines Alkylesters vorliegt.

3. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß das 13,14-Dihydro-15-keto-prostaglandin in Form einer 20-Alkylverbindung mit einer Alkylgruppe in der C-20-Stellung vorliegt.

4. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß das 13,14-Dihydro-15-keto-prostaglandin ein 13,14-Dihydro-15-keto-20-ethyl-prostaglandin ist.

5. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß das 13,14-Dihydro-15-keto-prostaglandin ein 13,14-Dihydro-15-keto-20-ethyl-prostaglandin F ist.

6. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß das 13,14-Dihydro-15-keto-prostaglandin ein 13,14-Dihydro-15-keto-20-ethyl-prostaglandin-$F_{2\alpha}$-isopropylester ist.

7. Verwendung von 13,14-Dihydro-15-keto-prostaglandin A, B, C, D, F oder J für die Herstellung eines Arzneimittels für die Behandlung von Glaukom.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung eines Mittels für Okularhypertonie, dadurch **gekennzeichnet,** daß ein 13,14-Dihydro-15-keto-prostaglandin A, B, C, D, F oder J und ein pharmazeutisch annehmbarer Träger dafür vermischt werden.

2. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß die Carboxylgruppe am Ende der α-Kette in dem 13,14-Dihydro-15-keto-prostaglandin in Form eines Alkylesters vorliegt.

3. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß das 13,14-Dihydro-15-keto-prostaglandin in Form einer 20-Alkylverbindung mit einer Alkylgruppe in der C-20-Stellung vorliegt.

4. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß das 13,14-Dihydro-15-keto-prostaglandin ein 13,14-Dihydro-15-keto-20-ethyl-prostaglandin ist.

5. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß das 13,14-Dihydro-15-keto-prostaglandin ein 13,14-Dihydro-15-keto-20-ethyl-prostaglandin F ist.

6. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß das 13,14-Dihydro-15-keto-prostaglandin ein 13,14-Dihydro-15-keto-20-ethyl-prostaglandin-$F_{2\alpha}$-isopropylester ist.

7. Verfahren zur Herstellung eines Mittels für die Behandlung von Glaukom, dadurch **gekennzeichnet,**

daß ein 13,14-Dihydro-15-keto-prostaglandin A, B, C, D, F oder J und ein pharmazeutisch annehmbarer Träger vermischt werden.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE

1. Utilisation des 13,14-dihydro-15-céto-prostaglandines A, B, C, D, F ou J pour la fabrication d'un médicament pour le traitement de l'hypertension oculaire.

2. Utilisation selon la revendication 1, dans laquelle le groupe carboxyle à l'extrémité de la chaîne a de la 13,14-dihydro-15-céto-prostaglandine est sous la forme d'un ester alkylique.

3. Utilisation selon la revendication 1, dans laquelle la 13,14-dihydro-15-céto-prostaglandine est sous la forme 20-alkyle, ayant un groupe alkyle à la position C-20.

4. Utilisation selon la revendication 1, dans laquelle la 13,14-dihydro-15-céto-prostaglandine est une 13,14-dihydro-15-céto-20-éthyl-prostaglandine.

5. Utilisation selon la revendication 1, dans laquelle la 13,14-dihydro-15-céto-prostaglandine est une 13,14-dihydro-15-céto-20-éthyl-prostaglandine F.

6. Utilisation selon la revendication 1, dans laquelle la 13,14-dihydro-15-céto-prostaglandine est une 13,14-dihydro-15-céto-20-éthyl-prostaglandine $F_{2\alpha}$, ester isopropylique.

7. Utilisation des 13,14-dihydro-15-céto-prostaglandines A, B, C, D, F ou J pour la fabrication d'un médicament pour le traitement du glaucome.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un agent hypotenseur oculaire comprenant le mélange d'une des 13,14-dihydro-15-céto-prostaglandines A, B, C, D, F ou J et d'un support pharmaceutiquement acceptable.

2. Procédé selon la revendication 1, dans lequel le groupe carboxyle à l'extrémité de la chaîne a dans la 13,14-dihydro-15-céto-prostaglandine est sous la forme d'un ester alkylique.

3. Procédé selon la revendication 1, dans lequel la 13,14-dihydro-15-céto-prostaglandine est sous la forme 20-alkyle, ayant un groupe alkyle à la position C-20.

4. Procédé selon la revendication 1, dans lequel la 13,14-dihydro-15-céto-prostaglandine est une 13,14-dihydro-15-céto-20-éthyl-prostaglandine.

5. Procédé selon la revendication 1, dans lequel la 13,14-dihydro-15-céto-prostaglandine est une 13,14-dihydro-15-céto-20-éthyl-prostaglandine F.

6. Procédé selon la revendication 1, dans lequel la 13,14-dihydro-15-céto-prostaglandine est une 13,14-dihydro-15-céto-20-éthyl-prostaglandine $F_{2\alpha}$, ester isopropylique.

7. Procédé de préparation d'un agent pour le traitement du glaucome, comprenant le mélange d'une des 13,14-dihydro-15-céto-prostaglandines A, B, C, D, F ou J et d'un support pharmaceutiquement acceptable.